REMARKS/ARGUMENTS

Status of the Claims

Upon entry of the present amendment, Claims 1, 3 and 10 are amended and Claims 12, 16 and 75 are canceled. Claims 19-30 and 33-74 are withdrawn.

Claim 1 has been amended to recite "at least 75% identical to the full-length of an amino acid sequence as set forth in SEQ ID NO:3" and "wherein said amino acid sequence comprises an ATP-binding cassette (ABC) family sterol transporter." Support is found, for example, in SEQ ID NOs: 1 and 3, on pages 72-74, and on page 3, lines 1-2 of the specification.

Claims 1 and 3 are amended to remove recitation of SEQ ID NOS: 5 and 6.

Claim 10 is amended to recite "a nucleotide sequence at least 80% identical to the full-length of a sequence as set forth in SEQ ID NO:4." Support is found, for example, in SEQ ID NOS: 2 and 4, on pages 72-75 of the specification.

Objection

The Examiner objects to Claims 1-18, 31, 32 and 75-77 for reciting SEQ ID NOS: 5 and 6. This objection is believed obviated by removing recitation of SEQ ID NOS: 5 and 6 from Claims 1 and 3. Claim 2 still recites SEQ ID NOS: 5 and 6, because polyclonal antibodies that specifically bind to amino acid sequences SEQ ID NOS: 5 and 6 expectedly would specifically bind to an amino acid sequence of SEQ ID NO:3.

Rejection under 35 U.S.C. § 101

Applicants respectfully traverse the rejection of Claims 1-18, 31, 32 and 75-77 as allegedly failing the utility requirement under 35 U.S.C. § 101, because the Examiner has not applied the appropriate standards in formulating this rejection. The Examiner asserts that "the claimed invention is not supported by either a credible asserted utility or a well-established utility" (Office Action mailed November 19, 2003 at page 2, paragraph 4, line 2), but presents arguments regarding specific and substantial utility, and concludes at the end of paragraph 4, that

"the claimed invention has no specific or substantial asserted utility" (Office Action mailed November 19, 2003 at page 3, paragraph 4, line 12).

The Examiner bases arguments on language quoted from page 9 of the present specification, but uses these statements in isolation of the rest of the specification and quotes them out of context. Any rejection based on lack of utility must be based on an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. M.P.E.P. § 2107(II)(C)(1)(iii) and (2)(iii).

The Standards

> An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible. M.P.E.P. § 2107 (II)(A)(3).
>
> If the applicant has *asserted* that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the *assertion* would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. M.P.E.P. § 2107 (II)(B)(1) (emphasis added).
>
> Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. M.P.E.P. § 2107 (II) at page 2100-31.
>
> Only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained. M.P.E.P. § 2107 (II) at page 2100-31.

Although the present claims are directed to nucleic acids, expression cassettes and cells comprising the nucleic acids and methods of using the nucleic acids to make SSG polypeptides, Example 3 of the *Revised Interim Utility Guidelines Training Materials* ("Utility Training Materials"), exemplifying therapeutic proteins, is instructive (pages 27-29).

Specific Utility

A 'specific utility' is *specific* to the subject matter claimed, as contrasted with a *general* utility that would be applicable to the broad class of the invention. M.P.E.P. § 2107.01 (emphasis in original).

In accordance with the definition for specific utility and the standard requiring *assertion* (as opposed to demonstration) of a specific utility, the specification asserts on page 3, lines 2-6 that the invention provides nucleic acids encoding a novel ABC family sterol transporter useful for the diagnosis and treatment of sterol-associated disorders, and for the identification of molecules that modulate the activity of SSG. The specification affirmatively states on page 8, lines 27-29 that SSG is involved in the transport of cholesterol and other sterols, across membranes, and is associated with the human disorder sitosterolemia.

The Examiner argues that the specification allegedly does not specifically demonstrate the **specific** function of the protein as an ATP-binding cassette (ABC) family sterol transporter or its relationship to any disease (bolding in original). This is not the standard. The requirement for specific utility is met by asserting that the nucleic acids encode an ABC family sterol transporter have a specific utility for the diagnosis and treatment of a sterol-associated disorder, such as sitosterolemia. The utility is specific because it depends upon the particular nucleic acid and the encoded protein sequences.

The Examiner's quotations of the text from page 9 of the specification are incomplete and taken out of context. The full sentence on page 9, lines 4-5 states that "it is speculated that SSG acts to effect sterol transport activity *as a monomer or, more preferably, as a homodimer or heterodimer* (emphasis added). The specification states at page 9, line 17 that the "SSG-ABC8 *heterodimer* is speculated to cause sterol, e.g., cholesterol, efflux from cells" (emphasis added). The specification never speculates that the SSG protein is an ABC family sterol transporter involved in sterol transport or that the SSG sequences are useful in the treatment and diagnosis of sterol-associated disorders. Whether the SSG protein operates as a monomer, homodimer or heterodimer is speculated, but the specification instructs at page 14,

lines 24-27 that SSG nucleic acids typically encode transporters that associate with heterologous ABC transporter proteins to form a heterodimeric transporter that acts to transport cholesterol out of cells.

In Example 3 of the Utility Training Materials, applicant's assertions that the claimed isolated protein had utility for curing Alzheimer's disease met the standard for specific utility because Alzheimer's is a well-known disease and the use depended upon the particular protein disclosed (Utility Training Materials at 28). Likewise, the presently asserted utility for the diagnosis and treatment of a sterol-associated disorder, such as sitosterolemia, is specific, because the utility depends upon the particular nucleic acid and the encoded protein sequences.

Substantial Utility

As with the standard for specific utility, the standard for substantial utility requires its assertion. M.P.E.P. § 2107 (II)(B)(1). A "substantial utility" defines a "real world" use. M.P.E.P. § 2107.01 at page 2100-32. The "real-world" use for the claimed nucleic acids is their application to the diagnosis and treatment of sterol-associated disorders, such as sitosterolemia (page 3, lines 2-6). With regard to treatment, the specification asserts that "by increasing SSG activity, it is possible to lower the absorption of dietary cholesterol and other sterols and to inhibit the development of foam cells. Such benefits can be achieved in any patient, e.g., to provide a treatment for sitosterolemia, hypercholesterolemia, atherosclerosis, coronary heart disease, hyperlipidemia, HDL deficiency, cholesterol gall stones, nutritional deficiencies, etc., or to prevent the development of any of these conditions in at risk patients" (page 9, lines 22-27).

In Example 3 of the Utility Training Materials, applicant's assertions that the claimed isolated protein had utility for curing Alzheimer's disease met the standard for substantial utility because a cure for Alzheimer's disease is a desirable outcome based upon a need in the art. Therefore, the disclosed use of the claimed protein was deemed substantial and "real world" (Utility Training Materials at 28). Likewise, the presently asserted utility for the

diagnosis and treatment of a sterol-associated disorder, such as sitosterolemia, is substantial, because the utility begets a desirable outcome based upon a need in the art.

Credible Utility

As set forth above, the Examiner "must treat as true a statement of fact made by an applicant in relation to an asserted utility, *unless* countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement." M.P.E.P. § 2107 (II) at page 2100-31 (emphasis added). Further, for a *prima facie* showing of no specific and substantial *credible* utility, the Examiner "must establish that it is *more likely than not* that a person skilled in the art would not consider credible any specific and substantial utility asserted by the applicant for the claimed invention." M.P.E.P. § 2107 (II)(C)(2) (emphasis added).

The specification asserts that a specific and substantial utility for the claimed nucleic acid sequences is for the diagnosis and treatment of sterol-associated disorders, including sitosterolemia, and for the identification of molecules that associate with and/or modulate the activity of SSG (page 3, lines 2-6). The specification supports this assertion with empirical evidence demonstrating that SSG mRNA expression, like ABC1 mRNA expression, is induced in the intestine by the LXR agonist, Compound A (Example E, page 70, lines 1-9 and Figure 1; Example H, page 70, line 26 through page 71, line 5 and Figure 3). The specification also demonstrates that LXR agonists Compounds B and C induce ABC1 and ABC8 expression in the human colon adenocarcinoma cell line Caco-2 (Example G, page 70, lines 20-25 and Figure 2), and that the LXR agonist Compound A stimulates cholesterol efflux from Caco-2 cells (Example I, page 71, lines 6-18 and Figure 4). Those of skill in the art can readily identify correlative inferences relating induction of increased SSG transcription to increased cholesterol efflux.

The specification expressly ties these inferences together. In the background section, the specification instructs that ABC1 and ABC8 (ABCG1) have been shown to transport cholesterol and other lipids, and that ABC8 is a "half site" family member, thought to require dimerization to function as a transporter (page 2, lines 8-15). Further, the specification relates as

background that mice lacking the LXRα receptor do not respond normally to increases in dietary cholesterol, establishing the essential role of LXRα in the regulation of cholesterol homeostasis (page 2, lines 25-28).

In the Introduction to the Description of the Specific Embodiments, Applicants explicitly set forth the inferences, based on accepted scientific principles, they believe can be drawn from the empirical data and from what was known by others. Applicants state that SSG nucleic acids and peptides are a novel member of the ABC family of transporter molecules (page 8, lines). This is based on shared sequence identity to *Drosophila* Brown protein, a member of the ABC superfamily (page 67, lines 12-13 and page 68, line 8). Because its increased transcription is induced by the LXRα agonist, Applicants inferred that SSG is involved in the transport of cholesterol and other sterols (page 8, lines 27-28). Further Applicants inferred that SSG binds to the ABC8 transporter to achieve sterol transport activity, and provided logical reasons: (i) both SSG and ABC8 belong to the subgroup of "half size transporters," which need to bind to additional ABC members for transport activity; (ii) both SSG and ABC8 are involved in sterol transport; (iii) SSG is homologous to the *Drosophila brown* and *scarlet* genes, and ABC8 is homologous to the *Drosophila white* gene, and, in *Drosophila*, the proteins encoded by *brown* and *scarlet* bind to the protein encoded by *white* (page 9, lines 4-13) It logically follows that SSG and ABC8 form a heterodimer involved in the transport of cholesterol. Therefore, mutations in the gene sequence encoding SSG that prevent formation of the heterodimer will prevent its sterol transport activity (page 9, lines 14-16). Accordingly, a loss of transporter activity leads to an increase in the absorption of dietary cholesterol and increasing SSG activity allows for lowering the absorption of dietary cholesterol (page 9, lines 20-27).

Empirical data that allow for correlative inferences can define a "real world" context of use in identifying potential candidates for preventative measures. M.P.E.P. § 2107.01 at 2100-21.[1] Importantly, the Examiner has not shown what countervailing evidence can be

[1] Stating that "[a]n assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. In example, the present invention employs *in vivo* and

provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of the assertions that the claimed SSG nucleic acid and amino acid sequences are useful in the diagnosis and treatment of sterol-associated disorders, including sitosterolemia. Further, the Examiner has not met his burden establishing that, more likely than not, a person skilled in the art would not consider credible the specific and substantial asserted utility that the claimed SSG nucleic acid and amino acid sequences are useful in the diagnosis and treatment of sterol-associated disorders, including sitosterolemia. The Examiner does not assert that the asserted utility is inconsistent with known scientific principles or incredible in light of the knowledge of the art.

In contrast to Example 3 in the Utility Training Material, Applicants have provided chemical, physical and biological properties of the SSG nucleic acid and amino acid sequences. Unlike Example 3, Applicants do not assert a utility of curing any disease, but assert a utility of diagnosis and treatment of sterol-associated disorders and the identification of molecules that associate with and/or modulate the activity of SSG. As further distinguished from Example 3, Applicants provide working Examples A-I that allow for meaningful correlative inferences, building upon what others knew about related ABC sterol-transport receptors and the essential role of LXRα in the regulation of cholesterol homeostasis. Applicants expressly articulate to those skilled in the art the logical inferences they believe can be drawn from the data in the specification and the information in the public domain. The subsequent publication in Science supports the credibility, as judged from those of skill in the art, of the asserted utilities for the claimed nucleic acid sequences (Berge, *et al.*, Science 290:1771 (2000)).

In view of the foregoing, Applicants respectfully assert that the present rejection under 35 U.S.C. § 101 is improper because the specification describes specific, substantial and credible utilities for the claim nucleic acid sequences. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

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in vitro cholesterol transport assays, described on page 52, line 13 through page 54, line 4 and in Example I, page 71, lines 6-18).

Rejection under 35 U.S.C. § 112, first paragraph, enablement requirement

The Examiner has rejected Claims 1-18, 31, 32 and 75-77 as allegedly failing the meet the enablement requirement under 35 U.S.C. § 112, first paragraph. Applicants respectfully traverse this rejection because the specification does reasonably provide enablement for isolated nucleic acids which encode an SSG polypeptide, wherein the nucleic acid is at least 80% identical to the full-length of SEQ ID NO:4 or wherein the encoded SSG polypeptide is at least 75% identical to the full-length of SEQ ID NO:3. Applicants further submit that the specification provides guidance to enable those skilled in the art to practice methods of making an SSG polypeptide, as is recited in Claims 31 and 32.

Claims 1-11, 13-15, 17-18 and 76-77 are directed to isolated nucleic acid sequences. Applicants have demonstrated how to make an isolated nucleic acid encoding an SSG polypeptide that is at least 75% identical to the full-length SEQ ID NO:3, as recited in independent Claim 1, because SEQ ID NO:3 (human SSG) and SEQ ID NO:1 (mouse SSG) are interspecies homologs that encode polypeptides sharing 78% identity (Exhibit B; *See also*, page 8, lines 19-20). Likewise, Applicants have also demonstrated how to make an isolated nucleic acid that is at least 80% identical to the full-length SEQ ID NO:4, as recited in Claim 10, because SEQ ID NO:4 (human SSG) and SEQ ID NO:2 (mouse SSG) share 82% identity (Exhibit A).

The Example section on page 66, line 21 through page 69, line 14 demonstrates how Applicants identified human SSG using well-known methodologies such as microarrays comprising EST libraries, standard cloning techniques, and public sequence databases. Applicants used the weak nucleic acid sequence identity between the *Drosophila brown* gene to the mouse SSG (SEQ ID NO:2) and human SSG (SEQ ID NO:4) sequences to identify mouse and human SSG coding sequences. In addition to using microarrays and computer databases, the specification teaches that nucleic acids encoding SSG homologs can be identified from, for example, genomic DNA libraries or expression libraries using techniques well-known to those in the art, including hybridization and amplification (*see*, page 29, line 1 through page 32, line 19).

Applicants have shown those of skill in the art how to make, without undue experimentation, an isolated nucleic acid that shares at least 80% sequence identity to the full-length of SEQ ID NO:4 and which encodes an SSG that shares at least 75% identity to the full-length of SEQ ID NO:3, for instance, by isolating an interspecies homolog.

The specification further teaches how to use the claimed isolated nucleic acids. As the specification teaches, the identified SSG variants have numerous uses related to the diagnosis and treatment of sterol-associated disorders, including sitosterolemia, hypercholesterolemia, atherosclerosis, coronary heart disease, hyperlipidemia, HDL deficiency, cholesterol gall stones, nutritional deficiencies (page 9, lines 22-27). The sequences also find use as research tools, for instance in the identification of molecules that associate with and/or modulate the activity of SSG (*see*, for example page 45, line 22 through page 59, line 28; *see also*, *Integra LifeSciences v. Merck*, 331 F.3d 860, 867 (recognizing the legitimacy of patented research tools)). Because the claimed nucleic acids have the testable function of encoding polypeptides that modulate transport of sterols such as cholesterol, they directly can be used to modulate the transcription and translation of SSG proteins and therefore modulate sterol (i.e., cholesterol) transport in a cell (see, page 52, line 13 through page 54, line 4, Example I on page 71, lines 6-18). The claimed nucleic acids also presently find use to identify modulators of SSG proteins, using methods well known to those in the art. The specification provides detailed guidance for assays for modulators of SSG proteins (page 45, line 22 through page 46, line 13; page 54, line 5 through page 59, line 28), assays for SSG-interacting compounds (page 46, line 14 through page 52, line 12), and assays for SSG protein activity (page 52, line 13 through page 54, line 4). Modulation of SSG transcription and/or expression can be significant for the treatment of numerous diseases, including sitosterolemia, atherosclerosis, hyperlipidemia, gall stones (e.g., cholesterol stones) hypercholesterolemia (e.g., familial hypercholesterolemia), coronary heart disease, HDL deficiency, nutritional deficiency, arthritis, xanthomas, and hemolytic anemia. (see, page 61, lines 1-8).

Claims 31 and 32, recite methods of making an SSG polypeptide. The specification teaches expression of the claimed SSG nucleic acid sequences on page 32, line 20

through page 35, line 20. Guidance for purification of SSG polypeptides is provided on page 35, line 21, through page 38, line 19.

For the foregoing reasons, Applicants respectfully submit that they have shown those of skill in the art how to make and use isolated nucleic acids encoding an SSG protein having at least 75% amino acid sequence identity to the full-length of SEQ ID NO:3, as recited in Claim 1, and nucleic acids sharing at least 80% nucleic acid sequence identity to the full-length of SEQ ID NO:4, as recited in Claim 10. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejection under 35 U.S.C. § 112, first paragraph, written description requirement

The Examiner has rejected Claims 1-18, 31, 32 and 75-77 as allegedly failing the written description requirement. Claims 12, 16 and 75 have been canceled. Applicants respectfully traverse this rejection because Applicants were in possession of the claimed isolated nucleic acid sequences, and because the SSG polypeptides encoded by the nucleic acid sequences share common structure and function.

The specification shows that Applicants were in possession of the claimed isolated nucleic acid sequences at the time of filing. Amended Claim 1 recites an isolated nucleic acid encoding an SSG polypeptide comprising an amino acid sequence that is at least 75% identical to the full-length of an amino acid sequence as set forth in SEQ ID NO: 3. Amended Claim 10 recites a nucleic acid sequence at least 80% identical to the full-length of a sequence as set forth in SEQ ID NO:4. Nucleic acid sequences SEQ ID NO:2 and SEQ ID NO:4 are interspecies homologs sharing at least 80% nucleic acid sequence identity,[2] which encode SSG polypeptides SEQ ID NO:1 and SEQ ID NO:3, respectively, sharing at least 75% amino acid sequence identity.[3]

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[2] Exhibit A (showing the BLAST2 (blastn) alignment of nucleic acid sequences SEQ ID NO:2 and SEQ ID NO:4). Sequences were inputted into the publicly available BLAST2 alignment algorithm at http://www.ncbi.nlm.nih.gov/blast/bl2seq/blast/bl2seq/bl2.html. Default settings were used.

[3] Exhibit B (showing the BLAST2 (blastp) alignment of amino acid sequences SEQ ID NO:1 and SEQ ID NO:3).

In accordance with the Examiner's suggestion, Claim 1 has been amended to recite "wherein said amino acid sequence comprises an ATP-binding cassette (ABC) family sterol transporter." Therefore, independent Claim 1 and claims incorporating the limitations of Claim 1 are not directed to any isolated nucleic acid sequence encoding a protein having at least 75% sequence identity to the full-length of SEQ ID NO:3, but to a nucleic acid sequence encoding an SSG polypeptide, which comprises an ATP-binding cassette (ABC) family sterol transporter. The recitation of an SSG polypeptide and an ABC family sterol transporter inherently defines particular structure and function. The claims recite a particular function by stating that the amino acid comprises an ABC family *sterol* transporter, and the specification teaches that SSG polypeptides are involved in the transport of cholesterol and other sterols, as well as other lipids, across membranes (page 8, lines 27-28). The claims also recite particular structure, because the claimed nucleic acid sequences encode an SSG polypeptide that shares at least 75% identity to the full-length of SEQ ID NO:3, and share structures common to SSG polypeptides and ABC family sterol transporters. The specification instructs, "the ATP binding cassette (ABC) family of transporters represent a large number of evolutionarily related transmembrane proteins that are involved in transport." The specification also teaches particular structural features of SSG polypeptides. "Structurally, the nucleotide sequence of SSG (see, e.g., SEQ ID NOs:1 or 3, isolated from mice and humans, respectively) encodes polypeptides comprising one ATP binding domain, one hydrophobic domain (comprising six transmembrane regions), a motif A or P loop, a motif B, and other signature sequences typical of ABC transporters" (page 12, lines 3-7).

Therefore, in accordance with the Examiner's concerns, Claim 1 and Claims 2-11, 13-15, 17-18, 31, 32 and 76-77 which incorporate the language of Claim 1, structurally and functionally define the claimed genus. Sequence alignments of SEQ ID NOS: 1 and 3 and SEQ ID NOS: 2 and 4 demonstrate that Applicants were objectively in possession of at least two representative interspecies homologs within the scope of the claimed invention.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

Eugenia Garrett-Wackowski
Reg. No. 37,330

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
Attachments
EGW:lls
60098453 v1

NCBI Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.6 [Apr-09-2003]

Match: 1 Mismatch: -2 gap open: 5 gap extension: 2

x_dropoff: 50 expect: 10.0000 wordsize: 11 Filter ☑ Align

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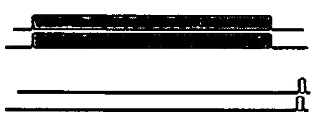
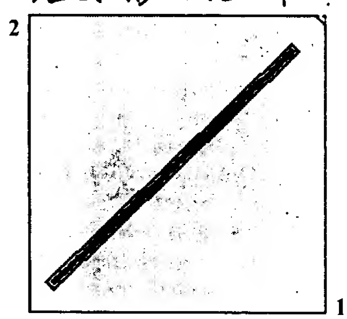
Sequence 2 lcl|seq_2 **Length** 2340 (1 .. 2340) SEQ ID NO: 4





NOTE:The statistics (bitscore and expect value) is calculated based on the size of nr database

NOTE:If protein translation is reversed, please repeat the search with reverse strand of the query sequence

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Identities = 1527/1852 (82%)
 Strand = Plus / Plus
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             |||||| ||| |||| |||| |||||  |||||| ||||||||||||||||||||||||
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Query: 275  atcgagagtggccagattatgtgcatcttaggcagctcaggctcagggaagaccacgctg 334
             | ||||| || ||||| ||||||||| |||| ||||||||||| ||||| |||||||||
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EXHIBIT

A

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            ||||| || || |||||||||||| |||| ||||| |  || ||||||||||||||||||
Sbjct: 1472 ggcctctaccagaagtggcagatgatgctggcctatgcactgcacgtcctccccttcagc 1531

Query: 1475 gtcatcgccacggtcattttcagcagtgtgtgttattggactctgggcttgtatcctgaa 1534
            ||  | |||||  | ||||||||||||||||| || ||||| ||||||||  |||||||
Sbjct: 1532 gttgttgccaccatgattttcagcagtgtgtgctactggacgctgggcttacatcctgag 1591

Query: 1535 gttgccagatttggatatttctctgctgctcttttggcccctcacttaattggagaattt 1594
            |||||| ||||||||||||| ||||||||||| |||||||| ||||||||||| ||||||
Sbjct: 1592 gttgcccgatttggatatttttctgctgctctcttggccccccacttaattggtgaattt 1651

Query: 1595 ctaacacttgtgctgcttggtatagtccaaaaccctaatattgtcaacagtatagtggct 1654
            ||||| |||||||| |||||||| |||||||| || ||||| ||||||||| ||||||||
Sbjct: 1652 ctaactcttgtgctacttggtatcgtccaaaatccaaatatagtcaacagtgtagtggct 1711

Query: 1655 ctgctcagcatctctgggctgcttattggatctggatttatcagaaacatacaagaaatg 1714
            |||||   |||  | ||| ||||| |||||||||||||  ||||||||||||||||||||
Sbjct: 1712 ctgctgtccattgcgggggtgcttgttggatctggattcctcagaaacatacaagaaatg 1771

Query: 1715 cccattcctttaaaaatcctgggttattttacattccaaaaatactgttgtgagattctc 1774
            ||||||||||| |||||| |  |||||||||||||||||||||| ||  ||||||||||
Sbjct: 1772 cccattccttttaaaatcatcagttattttacattccaaaaatattgcagtgagattctt 1831

Query: 1775 gtggtcaatgagttttacggcctgaacttcacttgtggtggatccaacacctctatgcta 1834
            || ||||||||||| ||||| ||||| |||||||||||  | || ||    ||| ||  |
Sbjct: 1832 gtagtcaatgagttctacggactgaatttcacttgtggcagctcaaatgtttctgtgaca 1891

Query: 1835 aatcacccgatgtgcgccatcacccaaggggtccagttcatcgagaaaacctgcccaggt 1894
            | | | || ||||| ||| |||| |||||  | || ||||| ||||||||||||||||||
Sbjct: 1892 actaatccaatgtgtgccttcactcaaggaattcaattcattgagaaaacctgcccaggt 1951

Query: 1895 gctacatccagattcacggcaaacttcctcatcttatatgggtttatcccagctctggtc 1954
            || ||||| ||||||||    ||||| || || || |||   ||||| |||||||| |||
Sbjct: 1952 gcaacatctagattcacaatgaactttctgattttgtattcatttattccagctcttgtc 2011

Query: 1955 atcctaggaatagtgatttttaaagtcagggactacctgattagcagatagt 2006
            ||||||||||||||  |||| ||| | |||||  | || |||||||| ||||
Sbjct: 2012 atcctaggaatagttgttttcaaaataagggatcatctcattagcaggtagt 2063

Score = 44.9 bits (23), Expect = 0.68
Identities = 35/41 (85%)
 Strand = Plus / Plus

Query: 2193 ttggacattgtgactgaactggtccaataatgtaaataata 2233
            ||||| ||||||||||| | |  |||| |||||||||||||
Sbjct: 2284 ttggaaattgtgactgagcggacccaagaatgtaaataata 2324

CPU time:     0.03 user secs.    0.00 sys. secs     0.03 total secs.

Lambda     K      H
    1.33    0.621     1.12

Gapped
Lambda     K      H
    1.33    0.621     1.12

Matrix: blastn matrix:1 -2
Gap Penalties: Existence: 5, Extension: 2
Number of Hits to DB: 11
Number of Sequences: 0
```

```
Number of extensions: 11
Number of successful extensions: 7
Number of sequences better than 10.0: 1
Number of HSP's better than 10.0 without gapping: 1
Number of HSP's successfully gapped in prelim test: 0
Number of HSP's that attempted gapping in prelim test: 0
Number of HSP's gapped (non-prelim): 5
length of query: 2258
length of database: 10,070,584,680
effective HSP length: 26
effective length of query: 2232
effective length of database: 10,070,584,654
effective search space: 22477544947728
effective search space used: 22477544947728
T: 0
A: 0
X1: 6 (11.5 bits)
X2: 26 (50.0 bits)
S1: 12 (23.8 bits)
S2: 21 (41.1 bits)
```

Blast 2 Sequences results

NCBI

PubMed Entrez BLAST OMIM Taxonomy Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.6 [Apr-09-2003]

Matrix BLOSUM62 gap open: 11 gap extension: 1

x_dropoff: 50 expect: 10.0000 wordsize: 3 Filter ☑ Align

Sequence 1 lcl|seq_1 **Length** 652 (1 .. 652) SEQ ID NO:1

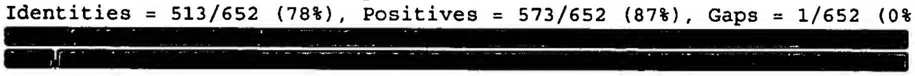
Sequence 2 lcl|seq_2 **Length** 651 (1 .. 651) SEQ ID NO:3

2

1

NOTE:The statistics (bitscore and expect value) is calculated based on the size of nr database

```
Score = 1035 bits (2677), Expect = 0.0
Identities = 513/652 (78%), Positives = 573/652 (87%), Gaps = 1/652 (0%)
```



```
Query: 1   MGELPFLSPEGARGPHINRGSLSSLEQGSVTGTEARHSLGVLHVSYSVSNRVGPWWNIKS 60
           MG+L  L+P G+ G  +NRGS SSLE    T  E  HSLG+LH SYSVS+RV PWW+I S
Sbjct: 1   MGDLSSLTPGGSMGLQVNRGSQSSLEGAPATAPEP-HSLGILHASYSVSHRVRPWWDITS 59

Query: 61  CQQKWDRQILKDVSLYIESGQIMCILGSSGSGKTTLLDAISGRLRRTGTLEGEVFVNGCE 120
           C+Q+W RQILKDVSLY+ESGQIMCILGSSGSGKTTLLDA+SGRL R GT  GEV+VNG
Sbjct: 60  CRQQWTRQILKDVSLYVESGQIMCILGSSGSGKTTLLDAMSGRLGRAGTFLGEVYVNGRA 119

Query: 121 LRRDQFQDCFSYVLQSDVFLSSLTVRETLRYTAMLALCRSSADFYNKKVEAVMTELSLSH 180
           LRR+QFQDCFSYVLQSD  LSSLTVRETL YTA+LA+ R +   + KKVEAVM ELSLSH
Sbjct: 120 LRREQFQDCFSYVLQSDTLLSSLTVRETLHYTALLAIRRGNPGSFQKKVEAVMAELSLSH 179

Query: 181 VADQMIGSYNFGGISSGERRRVSIAAQLLQDPKVMMLDEPTTGLDCMTANQIVLLLAELA 240
           VAD++IG+Y+ GGIS+GERRRVSIAAQLLQDPKVM+ DEPTTGLDCMTANQIV+LL ELA
Sbjct: 180 VADRLIGNYSLGGISTGERRRVSIAAQLLQDPKVMLFDEPTTGLDCMTANQIVVLLVELA 239

Query: 241 RRDRIVIVTIHQPRSELFQHFDKIAILTYGELVFCGTPEEMLGFFNNCGYPCPEHSNPFD 300
           RR+RIV++TIHQPRSELFQ FDKIAIL++GEL+FCGTP EML FFN+CGYPCPEHSNPFD
Sbjct: 240 RRNRIVVLTIHQPRSELFQLFDKIAILSFGELIFCGTPAEMLDFFNDCGYPCPEHSNPFD 299

Query: 301 FYMDLTSVDTQSREREIETYKRVQMLECAFKESDIYHKILENIERARYLKTLPMVPFKTK 360
           FYMDLTSVDTQS+EREIET KRVQM+E A+K+S I HK L+NIER ++LKTLPMVPFKTK
Sbjct: 300 FYMDLTSVDTQSKEREIETSKRVQMIESAYKKSAICHKTLKNIERMKHLKTLPMVPFKTK 359

Query: 361 DPPGMFGKLGVLLRRVTRNLMRNKQAVIMRLVQNLIMGLFLIFYLLRVQNNTLKGAVQDR 420
           D PG+F KLGVLLRRVTRNL+RNK AVI RL+QNLIMGLFL+F++LRV++N LKGA+QDR
Sbjct: 360 DSPGVFSKLGVLLRRVTRNLVRNKLAVITRLLQNLIMGLFLLFFVLRVRSNVLKGAIQDR 419

Query: 421 VGLLYQLVGATPYTGMLNAVNLFPMLRAVSDQESQDGLYHKWQMLLAYVLHVLPFSVIAT 480
           VGLLYQ VGATPYTGMLNAVNLFP+LRAVSDQESQDGLY KWQM+LAY LHVLPFSV+AT
Sbjct: 420 VGLLYQFVGATPYTGMLNAVNLFPVLRAVSDQESQDGLYQKWQMMLAYALHVLPFSVVAT 479

Query: 481 VIFSSVCYWTLGLYPEVARFGYFSAALLAPHLIGEFLTLVLLGIVQNPNIVNSIVAXXXX 540
           +IFSSVCYWTLGL+PEVARFGYFSAALLAPHLIGEFLTLVLLGIVQNPNIVNS+VA
Sbjct: 480 MIFSSVCYWTLGLHPEVARFGYFSAALLAPHLIGEFLTLVLLGIVQNPNIVNSVVALLSI 539
```

EXHIBIT

B

```
Query: 541 XXXXXXXXXXRNIQEMPIPLKILGYFTFQKYCCEILVVNEFYGLNFTCGGSNTSMLNHPM 600
                     RNIQEMPIP KI+ YFTFQKYC EILVVNEFYGLNFTCG SN S+   +PM
Sbjct: 540 AGVLVGSGFLRNIQEMPIPFKIISYFTFQKYCSEILVVNEFYGLNFTCGSSNVSVTTNPM 599

Query: 601 CAITQGVQFIEKTCPGATSRFTANFLILYGFIPALVILGIVIFKVRDYLISR 652
           CA TQG+QFIEKTCPGATSRFT NFLILY FIPALVILGIV+FK+RD+LISR
Sbjct: 600 CAFTQGIQFIEKTCPGATSRFTMNFLILYSFIPALVILGIVVFKIRDHLISR 651


CPU time:     0.03 user secs.     0.00 sys. secs      0.03 total secs.

Lambda      K       H
   0.325    0.141     0.421

Gapped
Lambda      K       H
   0.267   0.0410     0.140


Matrix: BLOSUM62
Gap Penalties: Existence: 11, Extension: 1
Number of Hits to DB: 3448
Number of Sequences: 0
Number of extensions: 238
Number of successful extensions: 2
Number of sequences better than 10.0: 1
Number of HSP's better than 10.0 without gapping: 1
Number of HSP's successfully gapped in prelim test: 0
Number of HSP's that attempted gapping in prelim test: 0
Number of HSP's gapped (non-prelim): 1
length of query: 652
length of database: 560,824,170
effective HSP length: 135
effective length of query: 517
effective length of database: 560,824,035
effective search space: 289946026095
effective search space used: 289946026095
T: 9
A: 40
X1: 15 ( 7.0 bits)
X2: 129 (49.7 bits)
X3: 129 (49.7 bits)
S1: 40 (21.6 bits)
S2: 79 (35.0 bits)
```